REMARKS

Currently Claims 1-16, 18-28, 55 and 56 are pending and stand rejected under the Office Action mailed March 7, 2007. Claims 4-5, 9, 17-18, 20, 22, 24-25 and 27 are withdrawn as being directed to a non-elected species, but depend from a generic claim. In view of the above amendment and the following remarks, reconsideration is respectfully requested.

Amendments to Claims

Claims 1 and 28 have each been amended to focus the claimed invention on the *intra*ocular administration of the claimed combinations of agents during intraocular ophthalmologic procedures. In view of the amendment, all independent claims are directed to intraocular delivery during intraocular ophthalmologic procedures. Dependent claims originally depending from Claim 1 have been amended to depend from Claim 55. Claim 56 has been cancelled to avoid redundancy in view of the amendment of Claim 1. New Claims 57-59 have been added to more fully claim the scope of the present invention, and are directed to methods of irrigating intraocular tissue during the intraocular procedure with a solution including one or more mydriatic agents and one or more anti-inflammatory agents.

Rejection under 35 USC § 103

Claims 1, 6 and 8 stand rejected under 35 USC § 103 based on US 5,523,316 to Gan et al. ("Gan") in combination with Arshinoff (1996) ("Arshinoff") and the Revision of Pharmacology (2002) ("ROP"). Gan, Arshinoff and ROP each disclose various ophthalmologic drug compositions or methods, and the Office Action concludes that the present invention merely claims the obvious use of drugs in an irrigation solution in a manner for which said drugs are routinely used in ophthalmologic procedures. Applicants respectfully traverse this rejection.

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a. The Claimed Invention

As discussed in greater detail, the cited references each fall far short of the claimed invention, and it would not be obvious to try to combine them. The present invention is directed to a method for perioperatively inhibiting ocular inflammation, inhibiting pain, effecting mydriasis, and/or decreasing intraocular pressure during an intraocular ophthalmologic procedure. The method comprises irrigating intraocular tissues during an intraocular ophthalmologic procedure with a solution including at least first and second agents in a liquid irrigation carrier. The first and second agents are selected to act on a plurality of differing molecular targets, each agent being selected from the physiologic functional classes of anti-inflammatory agents, analgesic agents, mydriatic agents and agents for decreasing intraocular pressure ("IOP reducing agents"), with the second agent providing at least one physiologic function different than a function or functions provided by the first agent. Independent Claims 1, 28 and 55 require that at least one of the first and second agents comprises a mydriatic agent or an IOP reducing agent. Independent Claim 57 more specifically calls for the first agent to comprise a mydriatic agent and the second agent to comprise an anti-inflammatory agent. Independent Claim 1 calls for continuous irrigation of the intraocular tissues during the procedure, while independent Claim 28 calls for each agent to being included at a concentration of no more than 100,000 nanomolar.

The present invention provides the benefit of addressing the need to inhibit pain, inhibit inflammation, maintain mydriasis and/or control intraocular pressure during an intraocular ophthalmologic procedure. Intraocular tissues are irrigated with a solution of agents selected to address these physiologic processes during the procedure. The present invention provides advantages over conventional techniques, which often may entail preoperative treatment with agents, such as to induce mydriasis, or postoperative treatment, such as to inhibit inflammation,

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pain or excessive intraocular pressure, or that address only a single one of these functions. The present invention provides an elegant solution to the shortcomings of potential diminished effect from preoperatively administered drugs that wash out or begin to wear off during the procedure, operative treatments that do not address all the physiologic functions needing to be addressed in connection with a procedure, topically applied drugs that are not administered directly to intraocular tissues, and postoperatively applied drugs that attempt to reverse physiologic processes that have already commenced during a procedure.

b. The Cited Art Does Not Provide the Solutions of the Claimed Invention

Gan discloses intraocular irrigation solutions including one or more drugs for controlling intraocular pressure in a BSS Plus® carrier solution. The drugs for controlling intraocular pressure include beta-blockers, alpha adrenergic agonists, muscarinic agonists, carbonic anhydrase inhibitors, angiostatic steroids and prostaglandins. As noted in prior responses, Gan does not teach combining IOP reducing agent(s) with another agent that is an anti-inflammatory, analgesic or mydriatic agent, as claimed. Gan is directed to irrigation solutions for controlling intraocular pressure, and not to the use of solutions of multiple agents selected to control multiple physiologic functions associated with ophthalmologic surgery. Gan also does not disclose continuous irrigation (Claim 1), concentrations of agents of no more than 100,000 nanomolar (Claim 28), or teach that mydriatic agents and anti-inflammatory agents should be included in the solution (Claim 57).

Arshinoff (1996) is a review discussing the use of drugs in connection with photorefractive keratectomy (PRK). Pharmacological treatment is discussed in the preoperative, intraoperative and postoperative periods of this procedure that entails reshaping of the cornea. Preoperatively before PRK, it is noted that topical anesthetics, miotics, NSAIDs, antibiotics and steroids may be used, though multi-drug combination therapy is not described. (Arshinoff at

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1038) Applicants note that miotics are used to cause contraction of the pupil, which is in contradistinction to the dilation of the pupil caused by mydriatics as claimed in various claims of the present invention. Arshinoff discloses that surgeons using one manufacturer's laser used preoperative miotics, while users of all other lasers preferred to operate on unconstricted pupils. (Arshinoff at 1040). Thus Arshinoff teaches that in PRK, miotics to contract the pupils may be used, but no mydriatics are used to dilate the pupil, contrary to aspects of the present invention.

Intraoperatively during PRK, Arshinoff discloses that 27% of surgeons work on a dry cornea, while the remaining 73% administer the same medications as preoperative (i.e., topical anesthetics, miotics, NSAIDs, antibiotics, steroids). (Arshinoff at 1038) There is no disclosure of any *intraocular* administration of drugs, which would not be required for this cornea procedure, nor any disclosure of the intraoperative administration of mydriatics or IOP reducing agents.

Postoperatively following PRK, Arshinoff discloses that *topical* NSAIDS may be utilized, and as noted in the Office Action also states that a combination of an NSAID with homatropine may be employed. This combination is disclosed as being administered topically and postoperatively only, not during the procedure and not intraocularly.

Arshinoff thus falls far short of the present invention. Finally, ROP discloses that NSAIDs can be used to inhibit miosis during cataract surgery, but this is disclosed only in the context of "topical" application of the NSAIDs. (ROP at 29).

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c. No Prima Facie Case of Obviousness

Applicants submit that each of Gan, Arshinoff and ROP is distinct from the present invention, for the reasons addressed above. As each is directed to different aspects of ophthalmologic procedures (controlling IOP in Gan, addressed PRK in Arshinoff, and cataract surgery is ROP), there is no reason to combine them other than Applicants' own disclosure. Moreover, Applicants respectfully submit that it would not be obvious to attempt to combine them, because of the risks potentially associated with administering drugs to the delicate structures of the eye. These potential risks argue against making such modifications in the absence of a road map such as Applicants' disclosure.

d. Art Teaches Away From the Invention

Applicants have included references with this Amendment that illustrate the above point, while also establishing that even if, for purposes of argument, a *prima facie* case of obviousness were provided by the hypothetical combination of cited references, the present application still claims patentable subject matter.

Applicants submit herewith a copy of Hirowatari et al., Reference ID O01832, which describes the results of a preoperative ophthalmic solution used prior to intraocular surgery. This solution includes an equal part mixture of 0.5% tropicamide/0.5% phenylephrine, 5% phenylephrine and 0.1% diclofenac, or TPD, that is applied *topically* and *preoperatively* at 120, 90, 60, 45, 30 and 15 minutes before surgery. (Hirowatari at 60). Hirowatari discloses that "Maximum mydriasis and corneal clarity during intraocular surgery are important to ensure operational safety. However, repeated instillation of mydriatic and anti-inflammatory ophthalmic solutions during surgery may affect compliance and may damage the corneal epithelium." Hirowatari, abstract. Hirowatari thus *teaches away* from the present claimed method of delivering combinations of agents by irrigating *intraocular* tissue *during* a procedure to

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perioperatively inhibit different physiologic functions associated with procedure, stating that preoperative topical treatment is preferred over intraoperative treatment.

Applicants also submit herewith a copy of Flach, Reference ID O01800, which describes the use of topically applied NSAIDs during cataract surgery and summarizes a review of 11 cases of corneal melting in patients treated with topical NSAIDs following cataract or other ophthalmologic surgical procedures. The paper concluded that inconsistent and variable dose-toxicity relationships suggested that coexistent factors other than simple drug toxicity were implicated in NSAID-associated corneal melting. Taken as a whole, Flach at a minimum is illustrative of the hazards that can arise from incorporating drugs into ophthalmologic surgical procedures, and demonstrates that adopting known drugs for use in connection with ophthalmologic procedures is not without risk or routinely undertaken as an obvious approach to modify surgical methods.

Applicants thus respectfully submit that the present invention provides a novel and nonobvious solution to shortcomings of conventional surgical techniques such as those described in the cited art.

Nonstatutory Obviousness-Type Double Patenting Rejection

Claims 1 and 28 were rejected for nonstatutory obviousness-type double patenting based on various claims of US Patents 6,261,279, 6,413,961 and 6,420,432, all in view of Gan, Arshinoff and ROP. Each of these noted US Patents was issued to inventors Demopulos et al. and assigned to the assignee of the current application. The Demopulos patents each claim perioperative methods for inhibiting pain and/or inflammation during surgical procedures, or solutions for inhibiting pain and/or inflammation, using one or a plurality of anti-inflammatory/anti-pain agents. The particular agents claimed vary for each of these patents. However, in all cases the agents claimed are anti-inflammatory and/or anti-pain agents. In no

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cases do the noted Demopulos patents claim the use of mydriatic agents or agents for reducing IOP, at least one of which mydriatic agents and IOP reducing agents is required in each of independent Claims 1 and 28.

Further, the methods of the presently pending claims would not be obvious over the claims of the Demopulos patents, which are directed solely to pain and inflammation and not to reducing IOP and/or promoting mydriasis as required by Claims 1 and 28. Consideration of Gan, Arshinoff and ROP do not change this outcome, because of the short comings of the cited references described above. Accordingly, it is respectfully submitted that present Claims 1 and 28 are not obvious over the claims of the commonly owned cited patents, alone or in view of the Gan, Arshinoff and ROP references.

Closure

In view of the above amendment and remarks addressing the new rejection, Applicants respectfully request reconsideration and allowance of all pending claims, inclusive of Claims 1-16, 18-28, 55 and 57-59. Should the Examiner have any questions or wish to discuss any matter, he is invited to telephone the undersigned attorney.

Respectfully Submitted,

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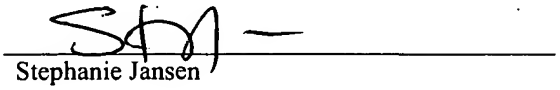

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